

## **REMARKS**

Applicants note with appreciation the acknowledgment of Applicants' claim for foreign priority based on an application filed in France on February 27, 1998. Applicants will file a certified copy of the application as required by 35 U.S.C. §119(b).

Applicants have amended Claims 1, 6, 8, 14, 16 and 18. Such clarifying amendments were primarily made to put the claims in a proper format, namely to avoid instances of lack of antecedence. Claim 1 has further been amended to substantially incorporate the subject matter of Claim 6 therein with the addition of subject matter from page 12, line 20.

Turning now to the merits, this invention relates to the delivery of active ingredients, particularly those that are hydrophobic, amphiphilic and/or insoluble, via a nanoparticle colloidal delivery system. The invention relates to new nanoparticles containing at least one active ingredient and one compound able to complex with at least one active ingredient. Particularly, the invention teaches the widening of the scope of use of polymers, especially polyalkylcyanoacrylates, by associating them with at least one compound able to complex with the active ingredients and increasing the active ingredient content in the nanoparticles.

### **Rejection Under 35 U.S.C. §102(e)**

Claims 1, 2, 6 - 8, 12, 13, 21, and 22 stand rejected as anticipated by U.S. Patent 5,641,515 to Ramtoola. Ramtoola discloses a controlled release pharmaceutical formulation wherein insulin is entrapped in a biodegradable polyalkylcyanoacrylate polymer to form nanoparticles, wherein the insulin is complexed to the

polyalkylcyanoacrylate. Ramtoola teaches that the rate of insulin release from the complexed nanoparticles is slower than that from corresponding free nanoparticles.

The nanoparticles of Claims 1, 2, 6 - 8, 12, 13, 21, and 22 are not anticipated by Ramtoola. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. This invention includes new nanoparticles which contain at least one active ingredient and, most significantly, at least one compound able to form a complex with the active ingredient, and a polymer (preferably polyalkylcyanoacrylate). This is taught by the Applicants at page 5 of the specification and elsewhere. The compounds capable of forming complexes with the active ingredient are cyclical oligosaccharides, the preferred embodiment of which is a cyclodextrin. Such a compound is not disclosed by Ramtoola. The resulting complex enables hydrophobic, amphiphilic and/or insoluble active ingredients to penetrate inside the polymer with the compound-active ingredient complex, resulting in a significant increase in encapsulation yield. Thus, Ramtoola discloses a two-component system, while Claims 1, 2, 6 - 8, 12, 13, 21, and 22 define a three-component system.

Ramtoola is further distinguished by reference to the specification. Applicants invite the Examiner's attention to page 7. Although Ramtoola describes encapsulation of insulin with a polyalkylcyanoacrylate polymer, such encapsulation is based on covalent bond formation between the active ingredient (insulin) and the polymer. This is sharply distinct from the claimed invention. Applicants describe formation of non-covalent, low-energy chemical bonds between the active ingredient and the compound able to complex with the active ingredient. The complexes of the invention result from an equilibrium

reached between the free-forms of the active ingredient and the compound and the complexes. As Applicants note:

The complexation of the active ingredient is implemented not only during preparation of the nanoparticle, but also in the prepared nanoparticles, in which it represents a means of associating a greater quantity of active ingredient.

In sum, since Ramtoola fails to disclose a three-component system or the use of a compound-active ingredient complexation to increase the encapsulation yield for more effective colloidal delivery of hydrophobic, amphiphilic and/or insoluble active ingredients, Ramtoola does not anticipate Claims 1, 2, 6 - 8, 12, 13, 21, and 22. Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §102(e).

**Rejection Under 35 U.S.C. §103(a)**

Claims 1, 2, 6 - 23 also stand rejected on the grounds of obviousness over Ramtoola. The Official Action alleges that those claims are *prima facie* obvious to one skilled in the art because Ramtoola teaches a controlled release formulation of nanoparticles where an active ingredient is complexed to a polyalkylcyanoacrylate polymer and that Ramtoola's methods of making the nanoparticles suggests the solicited process claims.

To establish a *prima facie* case of obviousness, there must be: a) some suggestion or motivation in the reference or within the skill of the art to modify the reference; b) reasonable expectation of success; and c) the prior art references must teach all of the claim limitations. MPEP 2143. The disclosure of the Ramtoola patent does not render the solicited claims *prima facie* obvious. Claims 1, 2 and 6 - 23 all recite a limitation not

found in Ramtoola, namely the presence of a compound able to complex with an active ingredient. Nothing in Ramtoola would suggest or motivate one skilled in the art to use a compound able to complex an active ingredient as the complexing agent rather than effecting encapsulation via direct complexation between the polymer and the active ingredient. In other words, there are no teachings or suggestions in Ramtoola to use three components instead of two components.

Ramtoola discloses only nanoparticles where the active ingredient is complexed with the polymer directly and that such nanoparticles are capable of releasing the bioactive active ingredient at a slower rate than free active ingredient-loaded polyalkylcyanoacrylate nanoparticles. It neither teaches the use of complexing agents, nor does it suggest complexation as a means to increase penetrability of hydrophobic, amphiphilic and/or insoluble active ingredients into nanoparticles delivery systems. Relying on the Ramtoola disclosure, a skilled artisan would have no basis to envision or practice the invention. For the same reasons, Ramtoola does not render obvious Claims 1, 2 and 6 - 23.

Claims 1 - 5 also stand rejected in view of Chen, et al. (U.S. Patent No. 5,932,248) and Trinh (U.S. Patent No. 5,246,611). We respectfully submit that this rejection is now moot in view of the amendment to Claim 1 with respect to the inclusion of the subject matter from Claim 6.

**Conclusion**

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. §102(e) and 35 U.S.C. § 103(a) are no longer applicable. Favorable consideration is respectfully requested.

Respectfully submitted,



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